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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,382	01/25/2001	Ian Richard Anselm Peak	8795-24 U1	6450

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PHILADELPHIA, PA 19103-7013

EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/771,382	PEAK ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,38,39 and 42-48* is/are pending in the application.

4a) Of the above claim(s) *42 and 43* is/are withdrawn from consideration.

5)☒ Claim(s) *33 and 34* is/are allowed.

6)☒ Claim(s) *38,39 and 44-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

JC

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 24, 2005 has been entered. Claims 1-32, 35-37 and 40-41 have been cancelled. Claims 38, 42 and 43 have been amended. Claims 47-48 have been added. Claims 42-43 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. It should be noted that the Examiner is examining SEQ ID NO: 11 (elected species) as well as SEQ ID Nos. 23 and 35.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 38-39, 44-46 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated proteins as set forth in SEQ ID NOs: 23 and 35 and compositions comprising the isolated proteins, does not reasonably provide enablement for proteins as set forth in SEQ ID NO: 11 or variants of SEQ ID NO:11, 23 or 35 or compositions comprising these proteins. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification broadly discloses a genus of polypeptides as set forth in SEQ ID NO:11. The specification teaches that SEQ ID NO: 11 is a consensus amino acid sequence (page 3). The specification teaches that SEQ ID NO:11 comprises constant regions of NhhA polypeptide designated as C1-C5 and non-conserved regions designated as V1-V-4 (page 3). The instant specification teaches that V1-V4 are non-conserved amino acids of a variable region (page 3). Therefore, the non-conserved regions of SEQ ID NO:11 can comprise any amino acid. Thus, the claimed polypeptide as set forth in SEQ ID NO:11 as well as variants of SEQ ID NOs. 23 and 35 can include any substitution or change of amino acids throughout regions V1-V4 of the polypeptide sequence. Therefore, SEQ ID No: 11 and variant or fragments of SEQ ID NOs: 23 and 35 can correspond to mutated sequences, allelic variants, splice variants, sequences that have a variant degree of identity (similarity, homology), and so forth are being claimed. There is no guidance provided as to which amino acids can be substituted, inserted or deleted and the polypeptide would retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's

amino acid sequence and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation. There is no guidance as to what amino acids may not be changed without causing a detrimental effect to the polypeptide being claimed. The claims broadly teach polypeptides which include substitutions and/or deletions, therefore any polypeptide is being claimed, and no specific location for the deletion, substitution or any combination thereof is recited. Thus, the resulting polypeptide could result in a polypeptide not taught nor enabled by the specification.

The claims of the instant application are not only drawn to isolated proteins but are also drawn to isolated proteins that have at least 80% or at least 90% identity to SEQ ID NOs. 23 and 25. Thus, the claimed isolated proteins include variants as well as fragments of SEQ ID NOs 23 and 35. There is no guidance provided in the specification as how one would begin to choose " variants or fragments" of SEQ ID NOs: 23 or 35. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does <u>not</u> disclose the following:

- the general tolerance to modification and extent of such tolerance;

- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which the retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties, 1984*", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Praline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach, 1989; pages 184-186*" teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "*Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Therefore, the specification fails to provide guidance regarding how to make and use polypeptides that fall within the broadly claimed genus of SEQ ID NO:11 that retain the claimed activity as well as how to make and use variants or fragments of SEQ ID NOs: 23 and 35.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting polypeptides that fall within the broadly claimed genus of consensus sequence SEQ ID NO:11 and variants or fragments of SEQ ID NOs: 23 and 35 having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral

level). One of skill in the art would require guidance, in order to make or use polypeptides that fall within the broadly claimed genus of SEQ ID NO: 11 or variants or fragments of SEQ ID NOs: 23 and 35 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 38-39 and 44-48 are rejected under 35 U.S.C. 102(a) as anticipated by Masignani et al *(WO 99/36544 published July 22, 1999).*

Claims 38-39 and 44-48 are drawn to an isolated protein consisting of at least one first region having an amino acid sequence selected from the group consisting of:

(i) residues 1 to 50 of SEQ ID NO:11;

(ii) residues 109 to 120 of SEQ ID NO:11

(iii) residues 144 to 198 of SEQ ID NO:11;

(iv) residues 221 to 239 of SEQ ID NO:11; and

(v) residues 249 to 604 of SEQ ID NO:11;

and at least one second region having an amino acid or amino acid sequence, the amino acid being (a) residue 51 of SEO ID NO:11- and the amino acid sequence being selected from the group consisting of:

(b) residues 52 to 54 of SEQ ID NO:11;

(c) residues 121 to 134 of SEQ ID NO:11;

(d) residues 199 to 220 of SEQ ID NO:11; and

(e) residues 240 to 248 of SEQ ID NO:11; wherein an Xaa residue in SEO ID NO:11 may be an absent amino acid or an amino acid residue at a corresponding position in any one of SEO ID NOS:1-10: and wherein upon administration to a mammal the isolated protein elicits an immune response against one or more strains of *N. meningitidis*.

Masignani et al teach proteins from *Neisseria meningitidis* and immunogenic compositions as well as pharmaceutical compositions containing the polypeptide (see the Abstract and pages 29-30). Masignani et al teach that fusion protein that can provide an alternative to direct protein expression (page 20). Masignani et al teach a protein (SEQ ID NO:5) consisting of a first region having for example (ii) amino acids 109 to 120 of SEQ ID NO: 11 and consisting of a second region having for example amino acids (a) 51 and (b) 52 to 54 of SEQ ID NO:11 or (c) amino acids 121 to 134 of SEQ ID NO:11 since amino acid residues 51 to 54 of SEQ ID NO: 11 and amino acids 121 to 134 of SEQ ID NO: 11 can be (Xaa) any amino acid (see sequence listing provide by Applicant filed 7/13/2001 and page 62 of the prior art). The protein and

pharmaceutical compositions of Masignani et al appear to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein and pharmaceutical compositions with the protein and pharmaceutical compositions of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein and pharmaceutical compositions of the prior art does not possess the same material structural and functional characteristics of the claimed protein and pharmaceutical compositions). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

4. Claims 38-39 and 44-48 are rejected under 35 U.S.C. 102(a) as anticipated by Peak et al *(WO 99/31132 published June 24, 1999).*

Claims 38-39 and 44-48 are drawn to an isolated protein consisting of at least one

first region having an amino acid sequence selected from the group consisting of:

(i) residues 1 to 50 of SEQ ID NO:11;

(ii) residues 109 to 120 of SEQ ID NO:11

(iii) residues 144 to 198 of SEQ ID NO:11;

(iv) residues 221 to 239 of SEQ ID NO:11; and

(v) residues 249 to 604 of SEQ ID NO:11;

and at least one second region having an amino acid or amino acid sequence, the amino acid being (a) residue 51 of SEO ID NO:11 and the amino acid sequence being selected from the group consisting of:

(b) residues 52 to 54 of SEQ ID NO:11;

(c) residues 121 to 134 of SEQ ID NO:11;

(d) residues 199 to 220 of SEQ ID NO:11; and

(e) residues 240 to 248 of SEQ ID NO:11; wherein an Xaa residue in SEO ID NO:11 may be an absent amino acid or an amino acid residue at a corresponding position in any one of SEO ID NOS:1-10: and wherein upon administration to a mammal the isolated protein elicits an immune response against one or more strains of *N. meningitidis.*

Peak et al teach proteins from *Neisseria meningitidis* and pharmaceutical compositions containing the polypeptide (see the Abstract and pages 34-40). Peak et al teach that fusion protein that can provide an alternative to direct protein expression (20-21). Peak et al teach a protein (SEQ ID NO:10) consisting of a first region having for example (i) amino acids 1 to 50 of SEQ ID NO: 11 or (ii) amino acids 109 to 120 of SEQ ID NO: 11 and consisting of a second region having for example (d) amino acids (a) 51 and (b) 52 to 54 of SEQ ID NO:11 or (c) amino acids 121 to 134 of SEQ ID NO: 11 since amino acid residues 51-to 54 of SEQ ID NO: 11 and amino acids 121 to 134 of SEQ ID NO: 11 can be (Xaa) any amino acid (see sequence listing provide by Applicant filed 7/13/2001 and pages xx-xxii of the prior art). The protein and pharmaceutical compositions of Peak et al appear to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein and pharmaceutical compositions with the protein and pharmaceutical compositions of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein and pharmaceutical compositions of the prior art does not possess the same material structural and functional characteristics of the claimed protein and pharmaceutical compositions). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

5. Claims 38-39 and 44-48 are rejected under 35 U.S.C. 102(e) as anticipated by Peak et al *(U. S. Patent No.6,197,312 B1 published March 2001).*

Claims 38-39 and 44-48 are drawn to an isolated protein consisting of at least one first region having an amino acid sequence selected from the group consisting of:

(i) residues 1 to 50 of SEQ ID NO:11;

(ii) residues 109 to 120 of SEQ ID NO:11

(iii) residues 144 to 198 of SEQ ID NO:11;

(iv) residues 221 to 239 of SEQ ID NO:11; and

(v) residues 249 to 604 of SEQ ID NO:11;

and at least one second region having an amino acid or amino acid sequence, the amino acid being (a) residue 51 of SEO ID NO:11 and the amino acid sequence being selected from the group consisting of:

(b) residues 52 to 54 of SEQ ID NO:11;

(c) residues 121 to 134 of SEQ ID NO:11;

(d) residues 199 to 220 of SEQ ID NO:11; and

(e) residues 240 to 248 of SEQ ID NO:11; wherein an Xaa residue in SEO ID NO:11 may be an absent amino acid or an amino acid residue at a corresponding position in any one of SEO ID NOS:1-10: and wherein upon administration to a mammal the isolated protein elicits an immune response against one or more strains of *N. meningitidis.*

Peak et al teach proteins from *Neisseria meningitidis* and pharmaceutical compositions containing the polypeptide (see the Abstract and columns 16-18). Peak et al teach that fusion protein that can provide an alternative to direct protein expression (columns 9-10). Peak et al teach a protein (SEQ ID NO:11) consisting of a first region having for example (i) amino acids 1 to 50 of SEQ ID NO; 11 or (ii) amino acids 109 to 120 of SEQ ID NO: 11 and consisting of a second region having for example (d) amino acids (a) 51 and (b) 52 to 54 of SEQ ID NO:11 or (c) amino acids 121 to 134 of SEQ ID NO: 11 since amino acid residues 51 to 54 of SEQ ID NO: 11 or amino acids 121 to 134 of SEQ ID NO: 11 can be (Xaa) any amino acid (see sequence listing provide by Applicant filed 7/13/2001 and columns 61-64 of the prior art). The protein and pharmaceutical compositions of Peak et al appear to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein and pharmaceutical compositions with the protein and pharmaceutical compositions of the prior art, the burden is on the applicant to show a

novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein and pharmaceutical compositions of the prior art does not possess the same material structural and functional characteristics of the claimed protein and pharmaceutical compositions). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Status of Claims

6. Claims 33 and 34 appear to be free of the cited prior art.

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
March 27, 2005

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